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Quantifying the heritability of task-related brain activation and performance during the N-back working memory task: A twin fMRI study

Gabriëlla A.M. Blokland [a,b,d], Katie L. McMahon [b], Jan Hoffman [b,e], Gu Zhu [a], Matthew Meredith [b], Nicholas G. Martin [a], Paul M. Thompson [c], Greig I. de Zubicaray [b,1], Margaret J. Wright [a,1,*]

[a] Genetic Epidemiology Laboratory, Queensland Institute of Medical Research, Brisbane, Australia
[b] Functional MRI Laboratory, Centre for Magnetic Resonance, University of Queensland, Brisbane, Australia
[c] Laboratory of Neuro Imaging, Department of Neurology, UCLA School of Medicine, Los Angeles, CA, USA
[d] Department of Biological Psychology, Free University, Amsterdam, The Netherlands
[e] Department of Biomedical Engineering, Hamburg University of Applied Sciences, Germany

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ABSTRACT

Working memory-related brain activation has been widely studied, and impaired activation patterns have been reported for several psychiatric disorders. We investigated whether variation in N-back working memory brain activation is genetically influenced in 60 pairs of twins, (29 monozygotic (MZ), 31 dizygotic (DZ); mean age 24.4 ± 1.7S.D.). Task-related brain response (BOLD percent signal difference of 2 minus 0-back) was measured in three regions of interest. Although statistical power was low due to the small sample size, for middle frontal gyrus, angular gyrus, and supramarginal gyrus, the MZ correlations were, in general, approximately twice those of the DZ pairs, with non-significant heritability estimates (14–30%) in the low-moderate range. Task performance was strongly influenced by genes (57–73%) and highly correlated with cognitive ability (0.44–0.55). This study, which will be expanded over the next 3 years, provides the first support that individual variation in working memory-related brain activation is to some extent influenced by genes.

1. Introduction

The localisation of task-related brain activity using fMRI, in particular during an N-back working memory task, has been used in a multitude of studies since the 1990s. Although these report somewhat mixed findings, inefficient or abnormal function is evident in several neurodegenerative (e.g., Wishart et al., 2004) and neuropsychiatric disorders (e.g., Matsuo et al., 2007; Callicott et al., 1998), and in the healthy siblings of patients for some disorders (e.g., Winterer et al., 2003). Deficits in physiological functions may therefore not only be associated with a disease, but also may reflect familial (possibly genetic) factors predisposing to the disorder. Further, fMRI studies have demonstrated that there are varied but reproducible individual patterns of brain activity, and group fMRI studies indicate a relationship between neural activity or metabolism in some brain regions and cognitive ability (Gray et al., 2003; Haier et al., 2003; Winterer et al., 2003; Duncan et al., 2000; for a review, see Gray and Thompson, 2004). However, except for two recent twin studies (Côté et al., 2007; Matthews et al., 2007), it is largely unknown to what extent individual differences in neural activity, as captured by fMRI, are influenced by genetic and environmental factors.

The present study investigates the heritability of brain activation during the N-back working memory task in a genetically informative sample. Twin studies investigating working memory performance have shown that individual variance in working memory function is moderately to highly heritable and that the covariance between working memory and general cognitive ability is largely determined by genes (e.g., Polderman et al., 2006; Ando et al., 2001; Luciano et al., 2001). Working memory has been described and discussed in various ways: as a cognitive system for the temporary storage and on-line manipulation of remembered information (e.g., Baddeley, 1986), as the type of memory that is active and only relevant for a short period (e.g., Fuster, 1995; Goldman-Rakic, 1995), and, most specifically, as the process by which a remembered stimulus is held "on-line" to guide behaviour in the absence of external cues or prompts (Goldman-Rakic, 1996). Thus, working memory is viewed as a fundamental set of processes, and an integral component of many cognitive opera-

* Corresponding author at: Genetic Epidemiology Laboratory, Queensland Institute of Medical Research, PO Royal Brisbane Hospital, Queensland 4029, Australia. Fax: +61 7 3362 0225.
E-mail address: margieW@qimr.edu.au (M.J. Wright).
[1] The authors wish it to be known that, in their opinion, the last two authors should be regarded as joint last authors.

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tions, from complex decision making to selective attention (Baddeley, 1986).

The variant of the N-back task used here has been employed in many previous fMRI studies, at several levels of investigation, and robustly engages multiple brain regions. The task requires on-line monitoring, updating, and manipulation of remembered information and is therefore assumed to place great demands on a number of key processes within working memory (Glahn et al., 2005; Owen et al., 2005). The frontal cortex, in particular the dorsolateral prefrontal cortex (DLPFC; approximate Brodmann areas 9/46), is routinely activated during the N-back (e.g., Jansma et al., 2000; Callicott et al., 1998; for reviews, see Owen et al., 2005; Owen, 2000, 1997; D'Esposito et al., 1998), and grey matter volumes in this region are highly heritable (Toga and Thompson, 2005). Other brain areas that are activated include the mid-ventrolateral frontal cortex, the frontal pole, the bilateral and medial premotor cortex, the bilateral and medial posterior parietal cortex, and the anterior cingulate cortex (reviewed by Owen et al., 2005).

Some initial reports have shown effects of specific genes on fMRI BOLD response during the N-back task (Egan et al., 2004, 2003, 2001), but the extent to which the total variance in task-related brain activation during working memory is influenced by genetic factors has not been investigated. Two recent twin studies using fMRI, the first focussing on sadness in a reasonably large sample (104 pairs) of 8-year-old twins (Côté et al., 2007), and the second using an interference processing task and a small sample of 20 female twin pairs (Matthews et al., 2007), suggest that there may be a modest, if any, genetic influence on neural activation, as captured by fMRI, and that the genetic contribution to individual differences in task-related brain activation may be both task specific and regionally variable. This is in contrast to twin studies using structural MRI that indicate there is a strong influence of genes on the volumes of brain structures, and on grey and white matter subvolumes; heritability of subcortical regions has been less well studied showing lower and more variable heritabilities (reviewed by Schmitt et al., 2007).

Here we use a sample consisting of 120 young adult twins to investigate the extent to which individual variation in task-related brain activation during the N-back task are attributable to genetic and environmental influences. In the twin design the inclusion of both monozygotic (MZ) and dizygotic (DZ)/fraternal twins enables the familial similarities in a trait to be parsed into genetic and shared environmental sources, with the remaining variance attributed to unique environmental factors, which includes measurement errors (Neale and Cardon, 1992). Phenotypic correlations between traits can be explicitly decomposed into common (shared) and specific (independent) sources of genetic and environmental variance. Our analyses focussed on three regions of interest (ROI) that have been repeatedly identified in previous studies, including the middle frontal gyrus, angular gyrus, and supramarginal gyrus. To map brain activation to anatomy, ROI were defined using an image-based probabilistic brain atlas based on a cytoarchitectonic cortical parcellation (Shattuck et al., 2008). This provides an explicit measure of the individual variability in macroanatomical structure at any coordinate, enabling activation in a voxel to be attributed to the most likely cytoarchitectonic area (Eickhoff et al., 2007), providing more accurate localisation than the widely used spherical ROI (Eickhoff et al., 2006). We also investigated the sources of variation in task performance, as well as the extent to which there was co-variation among the different brain regions, task performance, grey matter volume and general cognitive ability. These analyses represent the first in a series of studies to further our understanding of genetic mechanisms influencing variation in brain structure and function, which will provide new insights into individual differences in brain processing and vulnerability to brain disorders.

2. Method

2.1. Participants

Sixty pairs of twins, mean age 24.4 ± 1.7S.D. (range 21–27 years) and all right handed, participated in the study. They included 29 monozygotic (MZ) (14 female, 15 male) and 31 dizygotic (DZ) (14 female, 8 male, 9 opposite sex) twin pairs. All had previously participated in the Brisbane Twin Cognition study and had their general cognitive ability assessed using the Multidimensional Aptitude Battery (MAB), and zygosity determined by genotyping of 8–10 independent highly polymorphic DNA markers (PIC > 0.7) with a 99.99% probability of correct zygosity assignment (Wright and Martin, 2004). Twins were assessed for their suitability for imaging, and screened (by self-report) for significant medical, psychiatric or neurological conditions, including head injuries, a current or past diagnosis of substance abuse, and for current use of medication that was likely to affect cognition.

Sixty percent of the twins were scanned on the same day as their co-twin, with the remainder, on average, within 5 days of each other. This applied to both MZ and DZ twin pairs. The scanning session lasted 1 h 15 min, and each participant received a $100 gift voucher in appreciation of their time. The study was approved by the Human Research Ethics Committees of the Queensland Institute of Medical Research, University of Queensland, and Uniting Health Care, Wesley Hospital. Written informed consent was obtained for each participant.

2.2. N-back working memory task

Participants performed the 0- and 2-back versions of the N-back task based on Callicott et al. (1998, 1999, 2003a,b); see Fig. 1. In this task, a number (1–4, randomised) was presented in a fixed position in one of four large white circles, positioned at each of the corners of a diamond-shaped square, on a grey background. Stimuli were projected using an active video projector and presented on a screen at the foot of the scanner bed, viewed through a mirror placed above the participant's head. A fibre-optic response box, with four buttons arranged in the same configuration as the numbers presented on the screen, was used for responses. Participants, using their right index or middle finger, pressed one of the four buttons to match the target stimulus. For $n = 0$ (i.e., 0-back), the task required a simple button press in response to the number displayed. For $n = 2$ (i.e., 2-back), participants pressed the key corresponding to the number presented two trials before the current one. Thus the 2-back condition required both the maintenance of the last 2 numbers in memory and the updating of these remembered stimuli as each new stimulus was presented (Fletcher and Henson, 2001). While difficulty increased from 0-back to 2-back, the stimulus information and demands on response selection and execution were the same within levels.

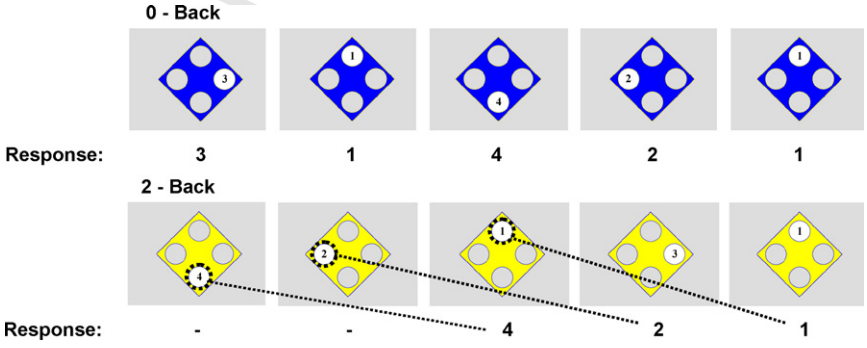

Fig. 1. The N-back task (adapted from Callicott et al., 2003a,b).

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Task levels were run in blocks with the level of the task shown on the screen, and the background colour of the diamond-shaped square changing from blue (0-back) to yellow (2-back) (Fig. 1). Participants were scanned through sixteen alternating blocks of the 0-back and 2-back conditions (i.e., 8 blocks/condition). Each block consisted of 16 trials, with a stimulus presentation time of 200 ms and an inter-stimulus interval of 800 ms. Thus the duration of each block was 16 s, resulting in a total experimental length of 4.16 min (256 s). Performance was measured as percentage of correct responses (accuracy) and response time (across correct trials) for each of the task conditions.

Participants were fully trained on the task prior to being positioned in the scanner, each performing a minimum of four training blocks (two per condition). The importance of effort and commitment to the task was emphasised. To acclimatise participants to the scanner and the response box, an additional set of practice trials were given once they were placed in the magnet, with the pulse sequence running in the background.

2.3. Image acquisition

Imaging was conducted on a 4 Tesla Bruker Medspec whole body scanner (Bruker, Germany) located at the Centre for Magnetic Resonance and Wesley Hospital MRI Research Facility in Brisbane. Images were acquired using a T2*-weighted gradient echo planar imaging (EPI) sequence, sensitive to blood oxygen level-dependent (BOLD) contrast (interleaved; repetition time TR = 2100 ms; echo time TE = 30 ms; flip angle = 90°; field of view FOV = 230 mm × 230 mm), and using a radio-frequency receive-transmit transverse electromagnetic head coil (MR-Devices, Vaughan, 1999). Geometric distortions in the EPI images caused by magnetic field inhomogeneities at high-field were corrected using a point-spread mapping approach (Zaitsev et al., 2003; Zeng and Constable, 2002). Over a continuous imaging run, we acquired 127 axial brain volumes, one volume every 2.1 s, with 36 coronal slices of 3 mm thickness (64 × 64 matrix; voxel size 3.6 mm × 3.6 mm × 3.0 mm), and with a 20% distance factor (0.6 mm slice gap). Head movement was limited by foam padding within the head coil, and a pulse oximeter was placed on the left index finger to monitor the participant. In the same imaging session, in addition to the functional scans, the following were also acquired: 3D T1-weighted images (MPRAGE, TR = 2500 ms; TE = 3.83 ms; T1 = 1500 ms; pulse angle = 15; coronal orientation; FOV 230 mm × 230 mm × 230 mm; matrix of 256 × 256 × 256) (Chou et al., 2008), ultra-high resolution T2-weighted images, and diffusion weighted images (Chiang et al., 2008).

2.4. Image processing

Images were processed and analysed using Statistical Parametric Mapping software (SPM5, Wellcome Department of Cognitive Neurology, London, UK; http://www.fil.ion./ucl.ac.uk/spm/; (Friston et al., 1999) implemented in MATLAB (The MathWorks Inc.). The first five EPI volumes were discarded to ensure that steady state tissue magnetisation was reached. Time-series volumes were realigned and unwarped using a robust rigid-body transformation procedure (Freire et al., 2002). A mean image generated during realignment was then coregistered with the participant's 3D T1 image, and the latter spatially normalised via non-linear basis functions to the standard T1 template image in MNI atlas space (Ashburner and Friston, 1999). The non-linear transformations were next applied to the time-series volumes from which the mean was generated. Normalised volumes were then re-sampled to 3 mm^3 voxels and smoothed with an 8 mm × 8 mm × 8-mm full width half maximum isotropic Gaussian kernel to control for inter-individual variance in regional anatomy. Global signal effects were estimated and removed using a voxel-level linear model (Macey et al., 2004). High pass (cut-off: 128 s) and low pass (AR1 model) filtering was applied to discard signals of no interest.

Image analysis was conducted in two stages, using block design fixed effects models at the single subject level and entering the resulting t-contrast images into a second-level group random effects model. Separate regressors were constructed for the 2- and 0-back conditions comprising a boxcar reference waveform convolved with a canonical haemodynamic response function (HRF). The specified contrast at the single subject level was "2-back > 0-back", representing the difference between the two conditions. The "2-back > 0-back" contrast images obtained for each participant were next entered into a group level (random effects) one-sample *t*-test, to identify the main effect of working memory for the entire sample (irrespective of zygosity). For the whole brain, significant activations were required to exceed a height threshold of $P < 0.05$ (FWE corrected for multiple comparisons) and cluster size threshold of 25 voxels.

An a priori region of interest (ROI) analysis was performed using the LONI Probabilistic Brain Atlas (LPBA40, Shattuck et al., 2008) in which the estimated grey matter probability density functions for each structure have been obtained through maximum likelihood computation of 40 subject volumes aligned to the Montreal Neurological Institute's 152 brains averaged T1 template. This provides an explicit measure of the individual variability in macroanatomical structure at any co-ordinate. Based on activation patterns found for spatial N-back tasks in previous studies (Callicott et al., 2003a,b, 2000, 1999, 1998; Egan et al., 2003; Weinberger et al., 1996), we selected ten ROI using a 50% probability threshold: middle frontal gyrus, angular gyrus, supramarginal gyrus, hippocampus, and cingulate gyrus, for

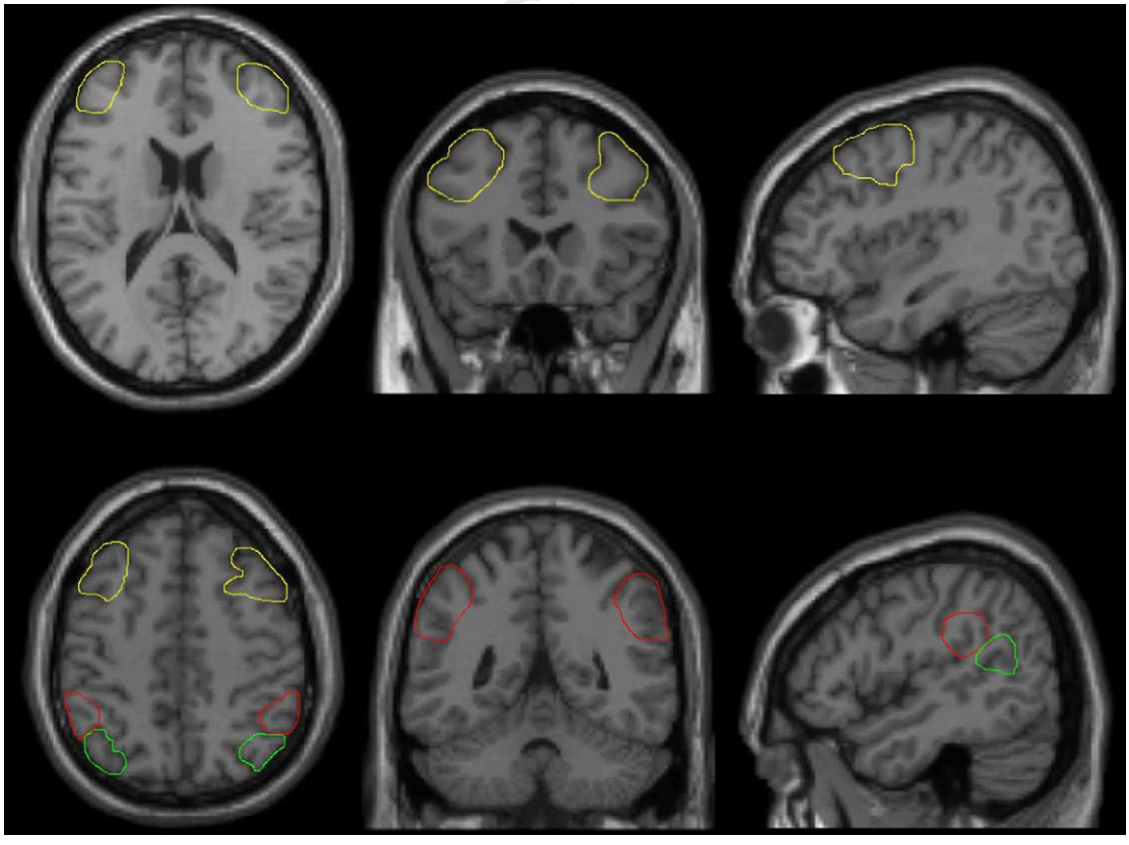

Fig. 2. Axial (a), coronal (b), and sagittal (c) views of ***a priori*** regions of interest (ROI) on a single-subject T1-weighted image. The ROI are 50% probability maps from the LPBA40 atlas (Shattuck et al., in press) of the middle frontal gyrus (in yellow) angular gyrus (in green) and supramarginal gyrus (in red).

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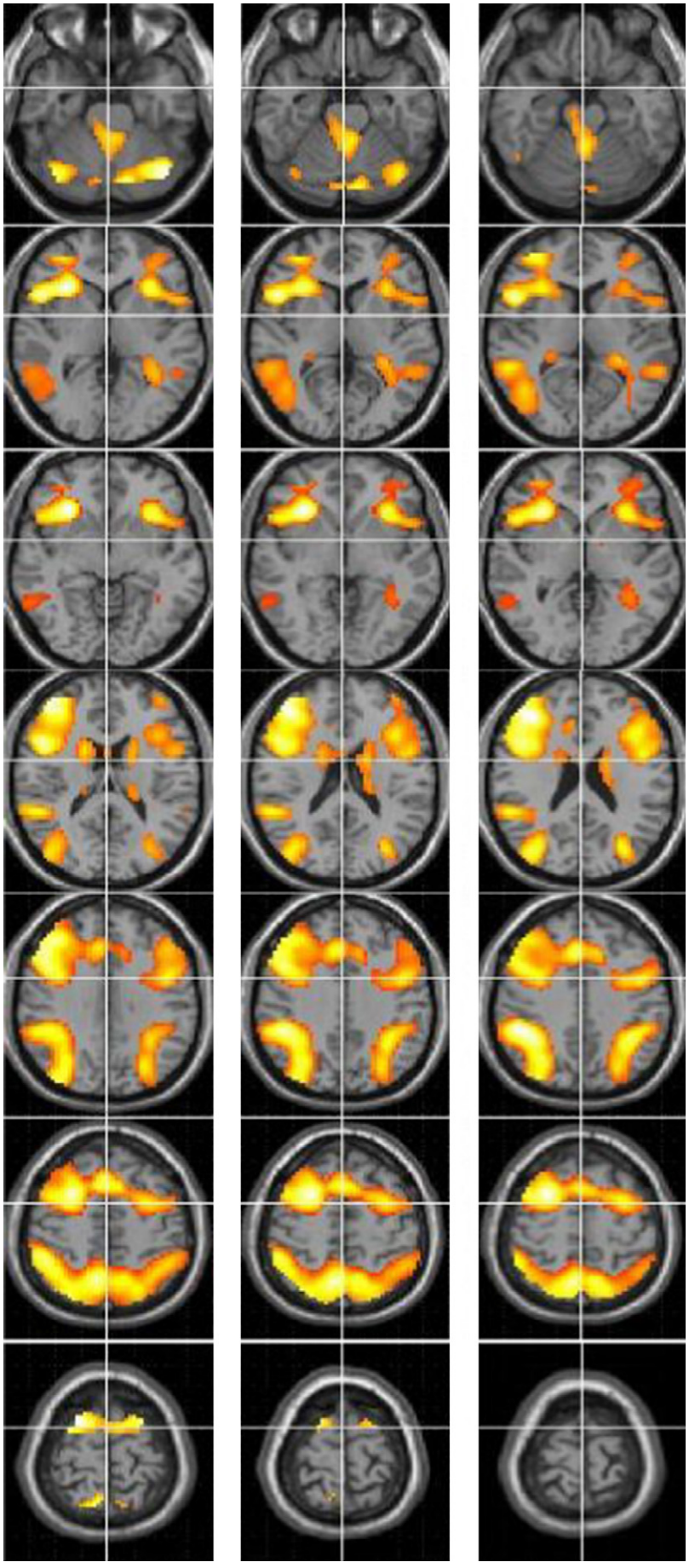

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Table 1
Mean (±S.D.) for N-back working memory brain activation (i.e. BOLD percent signal difference) and performance, Grey matter volume and Full-scale IQ

	MZ ($N = 58$)	DZ ($N = 62$)	Females ($N = 65$)	Males ($N = 55$)	Total ($N = 120$)
A priori Brain Regions					
Middle frontal gyrus (mfg)					
Left	0.32 (0.19)	0.35 (0.23)	0.34 (0.22)	0.33 (0.20)	0.34 (0.21)
Right	0.46 (0.23)	0.47 (0.23)	0.45 (0.23)	0.48 (0.22)	0.46 (0.23)
Supramarginal gyrus (smg)					
Left	0.28 (0.21)	0.19*(0.22)	0.26 (0.25)	0.20 (0.17)*	0.23 (0.22)
Right	0.35 (0.34)	0.32 (0.26)	0.34 (0.27)	0.32 (0.24)	0.33 (0.26)
Angular gyrus (ang)					
Left	0.34 (0.34)	0.27 (0.38)	0.24 (0.34)	0.38*(0.38)	0.30 (0.36)
Right	0.33 (0.24)	0.34 (0.28)	0.31 (0.29)	0.36 (0.22)	0.33 (0.26)
Task Performance:					
0-Back					
Accuracy (%)	81.7 (18.1)	86.3 (12.5)	81.9 (15.7)	86.7 (15.1)	84.1 (15.6)
RT (ms)	476 (70)	450* (61)	473 (64)	450 (68)	462 (66)
2-Back					
Accuracy (%)	68.3 (22.6)	62.5 (26.5)	60.4 (23.7)	71.1* (24.9)	65.3 (24.7)
RT (ms)	380 (100)	359 (110)	384 (107)	352 (102)	369 (105)
Grey matter volume (gmv)	0.88 (0.03)	0.88 (0.03)	0.88 (0.03)	0.88 (0.03)	0.88 (0.03)
FIQ (fiq)	113 (15)	110 (13)	109 (12)	116**(15)	112 (14)

*$P < .05$; **$P < .01$.

both left and right hemispheres. Within these a priori defined ROI, significant group level activations were required to exceed a small volume corrected (SVC) height threshold of $P < 0.05$ (FWE corrected for multiple comparisons within the volume of interest). Of these ten ROI, middle frontal gyrus, angular gyrus and supramarginal gyrus showed significant group activation irrespective of zygosity; the significant functional clusters were extracted yielding six phenotypic measures of brain activation related to working memory. Fig. 2 shows the outline of the 50% probability ROI on a single-subject T1-weighted scan.

We then employed the method used by Matthews et al. (2007) to extract, for each participant and each condition, the average percent BOLD signal across all voxels in each of the six significant functional clusters using the MARSBar Toolbox for SPM (Brett et al., 2002). This method proved to be superior to the extraction of local maximum signal intensity (*Z*-score) and spatial range (quantified as voxel count) for each ROI (Côté et al., 2007), where many cases (approximately 1/3 of the sample) of no suprathreshold activation ($P < .05$) were identified, and/or *Z*-scores reached ceiling.

In addition, total grey matter volume was calculated by segmenting the 3D T1 weighted images in SPM5.

2.5. Genetic modelling

In the classical twin design, the observed variance in a trait is typically decomposed into three possible sources of variance—additive genetic (A), common (shared) environmental (C), and unique or non-shared environmental (E) components, which include measurement error, differentiated by the relationships between factors for co-twins (Evans et al., 2002; Neale and Cardon, 1992). Variance due to genetic dominance (D) may also be estimated, but with MZ and DZ twins reared together it is not possible to determine the effects of both C and D in the same model; although one or other source can be assumed absent depending on whether the DZ twin correlation is greater ($d = 0$) or less ($c = 0$) than half the MZ correlation. Correlations between additive genetic factors are fixed at 1 for MZ twin pairs, as they share 100% of their genes, and 0.5 for DZ pairs as they share, on average, 50% of their genes. For common environmental factors (e.g., socioeconomic status or parental rearing style) correlations between co-twins are fixed at 1 for both MZ and DZ pairs, based on the rigorous and frequent testing that has supported the assumption that environments for MZ and DZ twins are comparable. By definition, non-shared environmental factors (e.g., illness, prenatal or postnatal traumas, peer groups) are left uncorrelated in twins.

Genetic modelling was performed using the statistical package Mx (Neale et al., 2002) to estimate the means, and genetic (A) and non-genetic (environmental (C and/or E)) components of variance via maximum likelihood (the likelihood of observing record *i*, given the population mean and variance and assuming normality), while also allowing for covariate effects on the means (Neale and Cardon, 1992). The dependent measures included: (1) task-related brain activation (i.e., 2-back minus 0-back BOLD percent signal) extracted from the six ROI; (2) task performance (accuracy and response time); and (3) grey matter volume. In addition, full-scale IQ was included, as estimated previously when participants were aged 16 (years). Univariate models examined the sources of variance for each of the measures, with sex included as a covariate (age was non-significant). The full ACE model was simplified by successive dropping of non-significant parameters, i.e., by seeing whether dropping a parameter resulted in a significant increase in the goodness-of-fit chi-square. We also calculated Akaike's information criteria (AIC), as chi-square minus 2 times degrees of freedom, which considers parsimony in addition to goodness of fit (Akaike, 1987). A bivariate ACE model examined the sources and pattern of covariation for left and right hemisphere for each task-related brain activation cluster, and specifically whether there were any common genetic influences.

Preliminary analyses examined differences in means and variances across groups (zygosity and sex). Where indicated, modelling included sex as a co-variate, and any zygosity differences in means and variances were left free to vary. Brain activation measures were normally distributed and did not require transformation. The distributions for both accuracy and response time for the 0-back condition were positively skewed, reflecting the low level of difficulty for this condition. Therefore, modelling was restricted to the 2-back condition for which both accuracy and response time were normally distributed. Grey matter volume and full-scale IQ were both normally distributed. Data were screened for outliers in both univariate and bivariate models but none were detected. Phenotypic correlations among measures and twin correlations and 95% confidence intervals were computed by maximum likelihood (ML).

3. Results

3.1. Task activation and performance

The random effect analysis showed a significant increase in BOLD signal during the 2-back compared to the 0-back condition (FWE, $P < .001$; see Fig. 3). Maintenance plus manipulation (2-back minus 0-back) significantly activated the middle frontal gyrus (including dorsolateral prefrontal cortex), cerebellum, fusiform gyrus, middle temporal gyrus, and parietal cortex. Participants were significantly less accurate on the 2-back compared to the 0-back condition, and response times were faster in the 2-back condition.

Table 1 shows the means and standard deviations for task-related brain response (i.e. BOLD percent signal difference) and performance measures, grey matter volume, and full-scale IQ. There were no mean differences or differences in variance between

Fig. 3. Main effect of the N-back working memory task. Results of the whole brain analysis of the 2 > 0-back contrast for the entire sample irrespective of zygosity, ($P < .05$, FWE corrected) shown on axial slices from a single subject's T1-weighted image in MNI atlas space.

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co-twins. Zygosity influenced some measures with the DZ group showing slightly less activation of the left supramarginal gyrus ($t = 2.26$, d.f. = 118, $P \leq .05$) and somewhat faster response times in the 0-back ($t = 2.23$, d.f. = 118, $P \leq .05$). Sex influenced activation of the left angular gyrus ($t = 2.19$, d.f. = 118, $P \leq .05$), accuracy in the 2-back ($t = -2.42$, d.f. = 118, $P \leq .05$), and full-scale IQ ($t = -2.76$, d.f. = 118, $P \leq .01$), with males having greater activation and performing slightly better (higher accuracy and IQ) than females respectively. Males also showed less variance in activation of the left supramarginal gyrus ($F(1, 119) = 7.55$, $P \leq .01$).

3.2. Phenotypic correlations among measures

For each task-related brain activation cluster, correlations between left and right hemisphere were in the moderate range (mfg = 0.56, ang = 0.46, smg = 0.53). There was also a low to moderate association among brain regions, which was generally higher for the right compared with the left hemisphere. Measures from the middle frontal gyrus were moderately correlated with both the angular gyrus (0.66 right; 0.41 left) and supramarginal gyrus (0.52; 0.41), and there was a low correlation between supramarginal and angular gyrus (0.33; 0.27). In addition, task performance measures, accuracy and response time, were moderately correlated (0.56) and both were moderately correlated with IQ (0.55 and 0.44 respectively). However, working memory brain activation did not correlate significantly with performance on the task, and grey matter volume did not correlate with either task-related brain activation or performance measures.

3.3. Twin correlations

Twin correlations are shown in Table 2. As the sample size is small, the confidence intervals were wide, and this is particularly evident for the brain activation measures. MZ correlations for both right angular gyrus and left middle frontal gyrus were significant and greater than the respective DZ correlation. For the remaining four ROI, both the MZ and DZ twin correlations were not statistically significant from zero. However, in general the MZ correlations were greater than the DZ correlations, providing an indication of additive genetic control of familial aggregation for task-related brain activation.

With respect to performance on the task, the MZ correlations for accuracy and response time were both significant and approximately twice those for the DZs. Similarly for grey matter volume both the MZ and DZ correlations were significant, with the MZ correlation double that for the DZs, and indicating a strong additive genetic influence. The twin correlations for IQ were in line with those found by us previously in a larger sample and suggesting a substantial genetic influence (Luciano et al., 2003).

3.4. Genetic modelling

Univariate ACE modelling estimated that 11–36.5% of the variance in task-related activation may be due to genetic factors (Table 2). Comparison of AE and CE models indicated an AE model provided a slightly better fit to the data for all six ROI, but with low statistical power due to the small sample size both the genetic (A) and shared environmental (C) variance components could be dropped from the saturated ACE model without a significant reduction in fit. For performance accuracy, IQ, and brain volume, an AE model provided the best fit to the data, with heritability estimates all in the moderate to high range (Table 2). For response time, either an AE or CE model was acceptable, with the AE model providing the better fit (Table 2).

Bivariate modelling, including left and right hemisphere for each region, which uses the additional information gained from the cross trait correlations to estimate common sources of variation between hemispheres, and can increase power for modelling, provided further indication that the variance in working memory brain activation may be partly due to genetic factors (Table 3). For all three regions, both the genetic and shared environmental variance components could be dropped from the full model, but the AE model provided a better fit than a CE model. In addition, for the middle frontal gyrus the AIC index of fit (the smaller the value the better the fit) indicated the AE a marginally better fit than the E model.

Table 2
Twin correlations (95% confidence intervals), univariate model fitting results, and percentage of variance estimates from the full ACE model

Phenotypes	Twin correlations (95% CIs)		Model fit: −2LL ($\Delta\chi^2$(Δd.f.), *P*-value)				ACE (%)†† estimates		
	MZ	DZ	ACE[a]	AE[b]	CE[b]	E[c]	A	C	E
Middle frontal gyrus									
Left	0.42* (*0.01, 0.67*)	0.10 (*−0.21, 0.38*)	335.40	335.40 (*0.00* (*1*), *ns*)	336.73 (*1.33* (*1*), *ns*)	339.27 (*3.87* (*2*), *ns*)	36.5	0.0	63.5
Right	0.21 (*−0.14, 0.50*)	0.12 (*−0.25, 0.44*)	336.94	336.94 (*0.00* (*1*), *ns*)	337.08 (*0.14* (*1*), *ns*)	338.75 (*1.81* (*2*), *ns*)	19.0	2.2	78.9
Angular gyrus									
Left	0.19 (*−0.20, 0.50*)	0.20 (*−0.14, 0.48*)	319.50	319.79 (*0.29* (*1*), *ns*)	319.50 (*0.00* (*1*), *ns*)	321.78 (*2.28* (*2*), *ns*)	0.0	19.3	80.7
Right	0.45* (*0.06, 0.68*)	−0.24 (*−0.50, 0.08*)	337.59	337.59 (*0.00* (*1*), *ns*)	338.54 (*0.95* (*1*), *ns*)	338.54 (*0.95* (*2*), *ns*)	18.6	0.0	81.4
Supramarginal gyrus									
Left	0.31 (*−0.08, 0.58*)	0.01 (*−0.33, 0.33*)	333.29	333.29 (*0.00* (*1*), *ns*)	334.11 (*0.82* (*1*), *ns*)	335.27 (*1.97* (*2*), *ns*)	24.2	0.0	75.8
Right	0.23 (*−0.14, 0.52*)	0.17 (*−0.17, 0.47*)	336.34	336.44 (*0.09* (*1*), *ns*)	336.39 (*0.05* (*1*), *ns*)	338.81 (*2.47* (*2*), *ns*)	11.0	11.8	77.2
2-back performance									
Accuracy	0.73** (*0.51, 0.85*)	0.31 (*−0.01, 0.56*)	311.18	311.18 (*0.00* (*1*), *ns*)	317.89 (*6.72* (*1*), *<.01*)	333.75 (*22.58* (*2*), *<.0001*)	72.9	0.0	27.2
Response time	0.57* (*0.26, 0.75*)	0.24 (*−0.09, 0.51*)	324.57	324.57 (*0.00* (*1*), *ns*)	327.25 (*2.69* (*1*), *ns*)	336.76 (*12.20* (*2*), *<.01*)	56.4	0.0	43.6
Grey matter volume	0.77** (*0.59, 0.87*)	0.43* (*0.09, 0.65*)	305.97	306.05 (*0.08*(*1*), *ns*)	312.30 (*6.33* (*1*), *<.05*)	338.16 (*32.19* (*2*), *<.0.001*)	69.0	8.1	23.0
Full-scale IQ	0.74** (*0.55, 0.85*)	0.27 (*−0.13, 0.57*)	303.41	303.41 (*0.00* (*1*), *ns*)	311.17 (*7.77* (*1*), *<.01*)	331.74 (*28.34* (*1*), *<.0001*)	73.6	0.0	26.4

Best fitting model is underlined. Nested sub-models are compared to the full ACE model by testing whether dropping a parameter resulted in a significant increase in the goodness-of-fit chi-squared (the difference in minus 2 times the log likelihood (−2LL) of a model and a nested submodel follows a chi-square distribution with degrees of freedom equal to the difference in the number of parameters). ††For both left and right middle frontal gyrus, angular gyrus, and supramarginal gyrus the parameter estimates for A and C are not statistically significant from zero due to low statistical power.
2LL = minus 2log-likelihood; $\Delta\chi^2$ = change in chi-square; Δd.f. = change in degrees of freedom. *$P < .05$; **$P < .01$.

[a] d.f. = 115.

[b] d.f. = 116.

[c] d.f. = 117.

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Table 3
Bi-variate model fitting results and genetic and non-genetic variance estimates (%) from the full ACE-ace model

Phenotypes	h^2	ACE-ace estimates (%)††									Bi-variate Model Fit: −2LL ($\Delta\chi^2$(Δd.f.), *P*-value) [*AIC*]			
		Common			Left			Right			ACE-ace[a]	AE-ae[b]	CE-ce[b]	E-e[c]
		A	C	E	a	c	e	a	c	e				
Middle frontal gyrus	30.2	18.1	0.0	38.2	20.5	0.0	23.2	3.8	0.0	39.9	627.01	627.01	630.69	633.20
												(0.00 (3), ns)	*(3.68 (3), ns)*	*(6.19 (6), ns)*
											[169.01]	*[163.01]*†	*[166.69]*	*[163.20]*
Angular gyrus	14.3	10.9	0.0	29.7	0.0	13.4	46.0	6.9	0.0	52.5	631.29	631.88	632.23	634.74
												(0.59 (3), ns)	*(0.94 (3), ns)*	*(3.45 (6), ns)*
											[173.29]	*[167.88]*	*[168.23]*	*[164.74]*
Supramarginal gyrus	22.0	19.4	0.0	31.1	5.1	0.0	44.4	0.0	6.2	43.3	633.62	633.72	634.40	637.43
												(0.10 (3), ns)	*(0.78 (3), ns)*	*(3.80 (6), ns)*
											[175.62]	*[169.72]*	*[170.40]*	*[167.43]*

Best fitting model is underlined. Nested sub-models are compared to the full ACE-ace model by testing whether dropping a parameter resulted in a significant increase in the goodness-of-fit chi-square (the difference in minus 2 times the log likelihood (−2LL) of any model and a nested submodel follows a chi-square distribution with degrees of freedom equal to the difference in the number of parameters). †Akaike Information Criterion (AIC) index of fit indicates the AE model is a slightly better than the E model. ††Based on the change in chi-square parameter estimates for A/a and C/c are not statistically significant from zero due to low statistical power.
2LL = minus 2 times the loglikelihood; $\Delta\chi^2$ = change in chi-square; Δd.f. = change in degrees of freedom; h^2 = heritability (i.e., total genetic variance).

[a] d.f. = 229.

[b] d.f. = 232.

[c] d.f. = 235.

4. Discussion

This study is the first to investigate the extent to which individual variation in brain activation, as captured by fMRI during an N-back working memory task, is influenced by genetic and environmental factors. Task-related brain activation (2 > 0-back) was indicated in the middle frontal gyrus (including dorsolateral prefrontal cortex), cerebellum, fusiform gyrus, middle temporal gyrus, and parietal cortex, as has been found in many previous studies, and participants were significantly less accurate but had faster response times on the 2-back compared to the 0-back condition. Six out of the ten ROI selected for analysis showed significant activation in the 2 > 0 back contrast, including left and right hemisphere for middle frontal gyrus, supramarginal gyrus, and angular gyrus. For these regions, MZ twin correlations for task-related brain activation were greater than the DZ correlations suggesting that individual variation in working memory activation is to some extent influenced by genes. Genetic modelling indicated a low to moderate heritability (14.3–30.2%) but with limited statistical power due to the relatively small sample size estimates were not significant. In addition to the neural correlates of working memory, we also assessed the extent of genetic and environmental influences on task performance. Accuracy on the 2-back condition was strongly influenced by genes with heritability (72.9%) similar in magnitude to both general cognitive ability (73.6%) and grey matter volume (69.0%), with genetic influences on 2-back response time shown to be in the moderate range (56.4%). Further, both accuracy and response time were significantly correlated with IQ (0.44–0.55), consistent with previous reports of a relationship between working memory and general cognitive ability.

The finding of a genetic influence, albeit suggestive, on working memory brain activation, is in line with behavioural studies showing that a significant proportion of the variance in working memory performance may be attributed to genes (Polderman et al., 2006; Ando et al., 2001; Luciano et al., 2001), as well as recent imaging work reporting the impact of polymorphisms, e.g. COMT and GRM7 on pre-frontal working memory function (Tan et al., 2007; Egan et al., 2004, 2003). The magnitude of the genetic influence on working memory brain activation appears to be somewhat more modest than for performance measures (i.e., 14.3–30.2% *cf.* >50%) as found here and reported previously. It is also considerably lower than that reported for lobar and overall brain volumes, and regional grey and white matter volumes, which in general have a high heritability (reviewed by Schmitt et al., 2007), as indicated here for total grey matter volume. However, our heritability estimates for task-related brain activation are comparable in magnitude to a recent study in which genetic influences accounted for 38% of the variance in activation of the dorsal anterior cingulate cortex during an interference task (Matthews et al., 2007). The only other fMRI study in a non-clinical twin sample, found no indication of a genetic influence on sadness, with both MZ and DZ twin correlations non-significant for two areas of the brain previously correlated with the subjective experience of sadness (Côté et al., 2007). While the present results and those of Matthews et al. (2007) are not sufficiently strong in themselves to indicate a role for genes on task-related brain activation, it is likely that, similar to behavioural measures, genetic influences may vary with task, as well as brain region and how brain activation/deactivation is quantified. The present study was similar to that of Matthews et al. (2007) in the use of a cognitive task (*cf.* an emotional task) and task-related BOLD fMRI. However, all three studies suggest that functional neuroimaging investigations in twins will likely require large samples in order to detect genetic influences.

An alternative explanation for the finding that MZ twins have more similar task-related brain activation is that MZ twins are more likely to use the same strategy to perform the task compared with DZ twins. The use of cognitive strategies has been shown to be correlated with task performance, and more recent strategy use during memory performance has been differentially associated with the activation of brain areas (Kirchhoff and Buckner, 2006; Spiers and Maguire, 2006). However it is not known whether there is a relation between the strategy adopted during an N-back task and differences in performance or brain regions recruited, or, more generally, whether strategy selection is genetically influenced, and whether any of the genetic variance in memory performance and/or brain activation is mediated by strategy use. While in the present study task performance was genetically influenced, for both MZ and DZ twins there was no correlation between task performance (accuracy and response time) and task-related BOLD signal, suggesting that the more similar task performance for MZ twins does not lead to more similarity in task-related brain activation.

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We found that a substantial part of the phenotypic variance in working memory brain activation was attributable to non-shared (unique) environmental influences. As a certain amount of non-shared environmental influences will include any errors of measurement, we are currently re-testing a subset of twins to investigate the extent that working memory-related BOLD signal increase is a stable trait. Previous studies show mixed findings with respect to test–retest reliability of fMRI, which are dependent on task, analysis methods, and regions of interest. For example, while high reliability (72% (same day); 63% (3–24 days) has been found for whole brain activation (number of voxels) during visual encoding (Machielsen et al., 2000) others have reported for multiple scans collected over a 2-month-period that there is large variability in the number of pixels activated during a basic motor task (e.g., in one slice, the worst case showed that only 18 pixels were consistently activated and the best case was 189 pixels) (Maitra et al., 2002). Similarly, whereas high reproducibility for BOLD fMRI in response to auditory oddball stimuli over a 6-week-period has been found (Kiehl and Liddle, 2003), an earlier study indicated that for different brain regions there is considerable variability in the reliability of both the position and number of activated voxels (Tegeler et al., 1999). Given the large estimate for non-shared environmental variance found here it is important to ascertain how much can be attributed to measurement error, because it places an upper limit on heritability estimates as the variance that is measurement specific is removed from the pool of variance that can be explained by genotype.

The phenotypic correlations between left and right hemisphere for each brain region were all in the moderate range suggesting some overlap in the sources of variance influencing bilateral activation of the regions. The bivariate analysis indicated a role for both common genetic and common non-shared environmental influences across hemispheres, with the overlap in non-shared environmental influences across hemispheres (29.7–38.2%) greater than the genetic influences (10.9–19.4%). Both genetic and environmental effects may be involved in generating functional relationships between bilateral regions, although some of the common non-shared environmental effects may reflect correlated measurement error. However, genetic (3.8–20.5%) and non-shared environmental (23.2–52.5%) influences specific to each hemisphere are equally important, accounting for approximately half of the variance in functional activation in each hemisphere.

The group analysis irrespective of zygosity showed significant activation across the sample in middle frontal gyrus, middle temporal gyrus, cerebellum, fusiform gyrus, and parietal cortex, but not the cingulate gyrus or hippocampus. Previous studies using the N-back task have shown reasonable consistency in the areas of activation (e.g., Callicott et al., 2003a,b, 2000, 1999, 1998; Egan et al., 2003; Weinberger et al., 1996), although a large number of them compared mean differences in activation/deactivation between patients (e.g., schizophrenia) and controls, rather than examining the effects of the task on brain activation. The finding here of no activation in the cingulate gyrus was not surprising as it has not been a consistent finding of the Callicott and Weinberger studies. However, as we used the entire cingulate gyrus from Shattuck et al. (2008), which might have been too conservative for the SVC, in a post hoc analysis we used the anterior portion of the cingulate, and found significant group activation in the 2 > 0 back contrast. We also calculated the twin correlations but there was no indication of a genetic influence on variation in task-related BOLD in the anterior cingulated (MZ = 0.19; DZ = 0.26).

Activation of the hippocampus has been reported in some studies, but the hippocampus is primarily involved in declarative and episodic memory rather than working memory (Eichenbaum, 1999; Tulving and Markowitsch, 1998). Also, we used a probabilistic atlas to attribute activation in a voxel to the most likely cytoarchitectonic area, compared with the use of single-subject atlases, which can be misleading for anatomical localisation in group data (Devlin and Poldrack, 2007; Toga and Thompson, 2007). Indeed, in comparing the hippocampal coordinates used by Egan et al. (2003) with the LONI probabilistic brain atlas that we used, most of the coordinates were not in the hippocampus, but more likely in the putamen, parahippocampal gyrus or middle temporal gyrus.

The finding of activation in the cerebellum, which was highly significant in the random effects group analysis, is interesting, and has also been indicated by the Callicott and Weinberger group. Cerebellar activation is generally associated with motor function, but the motor component during the 0-back and 2-back was the same. However, given that response times were significantly faster for the more demanding 2-back condition, activation of the cerebellum may be due to a difference in response preparation, since in the 2-back condition participants could prepare in advance which button to press. Alternatively, the processing demands of the 2-back may have induced faster responses so that the participant could update their working memory with the new stimulus to be remembered as fast as possible. There was no such demand in the 0-back. Indeed there are some indications that the cerebellum may play a role in higher cognitive (including working memory) and cognitive affective functions, and although still controversial (Konczak and Timmann, 2007) an increasing number of human lesion and functional brain imaging studies support the hypothesis that the cerebellum contributes to non-motor functions (Ravizza et al., 2006; Chen and Desmond, 2005).

Performance on the 2-back condition was found to be strongly influenced by genes, in particular accuracy (72.9%), but also response time which had a heritability of 56.4%. Previous studies have reported a low to moderate heritability for working memory performance (Polderman et al., 2006; Ando et al., 2001; Luciano et al., 2001), with some estimates for working memory speed found to be lower than those for working memory capacity (e.g., Neubauer et al., 2000). Given that heritability may increase with task complexity (Neubauer et al., 2000; Vernon, 1989), the high heritability for accuracy and response time found here suggest that the demands of the 2-back condition on working memory function may be greater than that of tasks used previously. We found large individual differences in both accuracy and response time on the 2-back, which can be quite difficult to perform well, and, given the relatively fast pace that stimuli were presented, the task requires a high level of concentration. Also, consistent with the general finding that working memory is moderately to strongly related to cognitive ability (e.g., Buehner et al., 2005), the phenotypic correlations between performance measures on the 2-back and IQ (accuracy: 0.55; response time: 0.44) were high and somewhat stronger than those reported in previous twin studies (0.20–0.41, Polderman et al., 2006; Ando et al., 2001; Luciano et al., 2001).

In summary, the findings of this study represent a first step in the assessment of genetic and environmental influences on working memory-related brain activation. While at this point the genetic influence on working memory brain activation should only be considered suggestive, there is a strong indication that as the sample size increases over the next 3 years, a significant genetic influence will be detected and a modest role for genes on neural activity during working memory established.

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